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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,170	07/20/2007	Gen-Sheng Feng	BURNHAM.010NP	7231
20995 7590 02/15/2011 KNOBBE MARTENS OLSON & BEAR LLP 2040 MAIN STREET FOURTEENTH FLOOR IRVINE, CA 92614			EXAMINER BERTOGLIO, VALARIE E	
			ART UNIT 1632	PAPER NUMBER
			NOTIFICATION DATE 02/15/2011	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com  
efiling@kmob.com  
eOAPilot@kmob.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/594,170	<b>Applicant(s)</b> FENG ET AL.	
	<b>Examiner</b> Valarie Bertoglio	<b>Art Unit</b> 1632	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 20 December 2010.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 7-12, 14, 26, 28-31, 44-52 is/are pending in the application.
- 4a) Of the above claim(s) 7-12 and 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26, 28-31 and 44-52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION

Applicant's reply filed on 12/20/2010 is acknowledged. Claims 1-6, 13,15-25,27,32-43 are cancelled. Claims 44-52 are added. Claims 7-12 and 14 are withdrawn. Claims 26,28-31,44-52 are under consideration.

### Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26 and 28-31 remain rejected and newly added claims 44-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a genetically modified mouse whose genome comprises a Shp2<sup>flox</sup> allele wherein the Shp2 gene is functionally disrupted in CamK2a-expressing cells such that no Shp2 is expressed in said cells and wherein said mouse exhibits increased body weight, early-onset obesity, and resistance to leptin, does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to genetically modified mouse comprising a disrupted Shp2 gene wherein said mouse is homozygous for said disrupted gene and exhibits increased body weight in comparison to a wildtype control mouse. Dependent claims recite additional phenotypes. The claims encompass mice that have a disruption in the Shp2 gene in all cells of the mouse or in cells other than cells of the forebrain.

The specification teaches a conditional knockout of the Shp2 gene in CamK2a-expressing forebrain cells (CaSKO mouse). The specification teaches use of a homologous recombination construct with loxP sites flanking exon 4 of the Shp2 gene to generate a line of mice (Shp2<sup>flox</sup>) that, when crossed to

Art Unit: 1632

a Cre-expressing line, will lose expression of Shp2 in Cre-expressing cells. Cre-mediated recombination results in deletion of exon4 and a frameshift that results to premature truncation. The specification teaches crossing the Shp2<sup>flox</sup> mouse to a mouse where the promoter driving expression of a Cre recombinase transgene is the CaMK2a promoter. The CaMK2a promoter drives expression only in the neurons of the hippocampus (see Reece 2004, page 388, provided herewith). The pattern of expression of the Cre recombinase determines which cell will lose expression of Shp2, which will then determine the phenotype of the mouse. The specification has taught only the CaSKO mouse lacking Shp2 in CaMK2a expressing cells. The specification has not taught other mice encompassed by the claims.

The art has demonstrated other conditional knockouts of the Shp2 gene wherein loss of Shp2 expression from other cells types, resulting from use of different promoters driving Cre expression, leads to phenotypes other than those claimed and disclosed in the specification (for example, see Grossman, PNAS. 2009, 106:16704-16709; Nakamura, PNAS, 2009, 106:11270-11275). The art has also demonstrated that a non-conditional knockout of Shp2 in all cells of a mouse is embryonic lethal (Saxton, 1997, EMBO J, 16:2352-2364). Therefore, the specification enables making only a mouse lacking Shp2 expression in CaMK2a-expressing cells with the claimed phenotypes. The phenotypes of other Shp2-disrupted mice would differ from those of the mice disclosed in the specification for the CaSKO mouse and therefore, the specification fails to enable those other mice encompassed by the claims.

Therefore, because the specification only teaches use of the CaMK2a promoter to drive Cre-mediated recombination to knockout the Shp2 gene in forebrain cells to obtain a mouse with the claimed phenotypes, and because loss of Shp2 activity in other cells results in other phenotypes, including lethality, the specification fails to enable any mouse other than a genetically modified mouse whose genome comprises a Shp2<sup>flox</sup> allele wherein the Shp2 gene is functionally disrupted in CamK2a-expressing cells such that no Shp2 is expressed in said cells and wherein said mouse exhibits increased body weight, early-onset obesity, and resistance to leptin.

Art Unit: 1632

Applicant has amended the claims to require that Shp2 not be expressed in the forebrain. This encompasses any and all cells of the forebrain, not just CaMK2a-expressing cells. Applicant remarks that the CaMK2a promoter does not drive expression only in the neurons of the hippocampus as discussed in the office action dated 08/19/2010. Applicant states that the Reece reference, which states at page 388, that the CaMK2a promoter drives expression only in the neurons of the hippocampus, was not provided. In response, this reference was provided along with the office action mailed 08/19/2010 and should be accessible via PAIR. Applicant's argument is not supported with any evidence of other expression patterns related to the CaMK2a promoter that would overcome the instant rejection. Evidence demonstrating that this promoter is expressed in all forebrain cells is necessary to address the rejection, given the teachings of Reece and the analysis set forth above.

Additionally, the claims as amended and added, encompass mice where the deletion is in any and all cells of the mouse, In addition to the forebrain. These mice are not enabled for reasons set forth above. Applicant's have not addressed this aspect of the rejection.

The rejection of claims 33-43 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is rendered moot by the cancellation of the relevant claims.

The rejection of claims 33-43 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is rendered moot by the cancellation of the relevant claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1632

The rejection of claims 36-37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is rendered moot by the cancellation of the relevant claims.

### **Conclusion**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1632

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/  
Primary Examiner, Art Unit 1632